# When to perform a bronchial challenge with mannitol?

## Quando effettuare un test di stimolazione bronchiale con mannitolo?

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Variable airflow limitation can be diagnosed by spirometry in asthmatic patients or provoked in a lung function laboratory by getting patients to inhale substances that induce bronchoconstriction, so making it possible to detect and measure the airway hyperresponsiveness (AHR) frequently associated with the diagnosis of asthma and its symptoms [1,2]. The intensity of AHR presents wide variability in individuals in general and particularly in asthmatic subjects, where the degree of AHR correlates with the airway inflammation and the severity of the disease [3,4].

Airway reactivity can be assessed with either direct or indirect stimuli. In the former case, methacholine or histamine, that directly act on airways smooth muscle, are usually employed [5], while prostaglandin $D_2$ or leukotrienes are mostly used for research purposes. The latter (indirect stimuli) include not only pharmacological agents such as adenosine monophosphate (AMP) or propranolol, sulphur dioxide, sodium metabisulphite, ozone, tachykinins and platelet activating factor (generally used in research trials), but also physical stimuli such as exercise, eucapnic hyperpnea of dry air, distilled water, hypertonic saline, and mannitol. These indirect stimuli determine airflow limitation by stimulating inflammatory cells, epithelial cells and nerves to release mediators that act on specific receptors of the smooth muscle and induce its contraction with resultant airway narrowing, and they can also determine a microvascular leakage [1,6,7].

Mannitol challenge is included in the category of osmotic aerosols, whose main reference is hypertonic saline, an easy to perform test that causes increased airways osmolarity and delivery of histamine from mast cells; it also shows a good correlation with the level of bronchial inflammation [8-10]. Bronchial challenge with inhalation of mannitol dry powder is not very new, since it was introduced in 1997 by Anderson and coworkers [11]; nevertheless it is not so widely used as the direct challenges with methacholine or histamine.

Bronchial challenge with directly stimulating agents shows high sensitivity for diagnosing asthma due to the high negative predictive value, while it has low specificity to distinguish between asthmatic and normal subjects or patients affected with chronic airflow limitation [6].

On the contrary, physical stimuli are more specific than methacholine or histamine to distinguish between asthmatic and normal subjects, but their sensitivity is relatively low compared with direct agents [12-14]. Thus, the direct challenges are the choice method to exclude current asthma, whereas the indirect ones are indicated to confirm the presence of asthma, especially when it is induced by exercise [15].

Mannitol shows a good correlation with other indirect stimuli such as exercise, hypertonic solutions and eucapnic hyperventilation [11,16] and it is not limited by physiologic factors as are other indirect challenges, namely exercise and eucapnic hyperventilation [6]. Mannitol test has also shown similar effects as AMP challenge; thus the two tests are to some extent interchangeable [17].

When given as a dry powder, mannitol increases the osmolarity of the bronchial mucosa that in turn causes the release from mastcells and also from eosinophils of histamine, prostaglandins and leukotrienes both in asthmatics and, to a much less-

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er degree, in normal subjects [18-20]. Furthermore, a correlation has been found between the level of bronchial hyperresponsiveness revealed by the mannitol challenge and the amount of eosinophils in sputum of asthmatic patients not treated with inhaled steroids [21].

The technique of mannitol bronchial challenge is very easy to perform, safe and less time consuming than other indirect tests, and it consists in delivering increasing doses of the osmotic substance through a dry-powder inhaler, recording the $FEV_1$ value 1 minute after each inhalation. The response is considered positive when a 15% fall in $FEV_1$ compared to baseline is obtained after inhaling a cumulative dose ($PD_{15}$) of mannitol of 635 mg or less [11,22,23]. This technique also allows to collect bronchial secretions (that increase when mannitol is administered), which can be examined for the presence of inflammatory cells [24].

So, what is the *rationale* for using mannitol in bronchial challenges?

The main usefulness of the challenge with mannitol is that it allows, in patients who have current symptoms of asthma, to confirm or exclude the presence of the disease, whereas a negative methacholine result is particularly valuable to rule out a diagnosis of asthma. Furthermore, the mannitol test seems particularly useful in patients affected with active asthma, where a high level of hyperreactivity as revealed by mannitol $PD_{15}$ is evidence of current airway inflammation, which highlights the need for treatment able to counteract inflammatory cells and their mediators, e.g. inhaled steroids, antihistaminic and anti-leukotrienes compounds. However, it should be borne in mind that the mannitol challenge, as other indirect and direct stimuli, fails to confirm asthma in about 30% of subjects with mild symptoms and bronchial inflammation; in some of these patients other diagnoses must be investigated [7,23]. Nevertheless, the mannitol challenge appears a valuable method to monitor the inflammation and the outcome of the disease in asthmatic patients during treatment with antinflammatory drugs. It may also be useful in a work or occupational setting to reveal possible sensitization to professional agents, and in athletes that present airway hyperresponsiveness after strenuous exercise, to confirm or exclude the presence of airway inflammation [25].

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